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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,824	09/16/2003	Christian Frisch	49974-023US	2286

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	**PAPER NUMBER**
1637	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/662,824	FRISCH ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 5, 2009 has been entered.

Claim Status

2. Applicant has cancelled claims 1-39, 41-45; amended claim 40. Only claims 40 is pending and will be examined in this action.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a

later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ge et al. (1995) Expressing Antibodies in *Escherichia coli* chapter 8 pp 229-266 (in Antibody Engineering edited by Carl A.K. Borebaeck. Oxford university Press New York) as evidenced by information obtained from Wikipedia about sizes of different Ig fragments that references Janeway CA, Jr *et al* (2001). *Immunobiology.* (5th ed.). Garland Publishing. ISBN 0-8153-3642-X and Krebber et al. (1997) J. Mol. Biol. Vol. 268: pp 607-618 (previously cited).

6. Regarding claim 40, Ge et al. teach a generally applicable method for the high volume expression of (poly)peptides/proteins encoded by genomic DNA fragments or expressed sequence tags (ESTs) comprising (see title expressing antibodies in *E. coli.* Also see page 229 par. 1 where methodology for cloning expressing, purifying recombinant antibodies in *E. coli* is taught. Thus Ge et al. teach a generally applicable method for the high volume expression of (poly)peptides/proteins. Also see page 230 where section Choice of the antibody fragment to be expressed, where antibody fragments are taught. Also see Fig. 8-1 in page 230 where fragments of antibodies are taught. Thus by teaching antibody fragment Ge et al. teach genomic DNA fragments):

(a) expressing a nucleic acid molecule encoding a fusion protein in the cytosol of E. Coli under conditions that allow the formation of inclusion bodies comprising said fusion protein (See page 233, Figure 8-2 (c) and the description

of above fig. where expressing a nucleic acid molecule encoding a fusion protein in the cytosol of E. Coli under conditions that allow the formation of inclusion bodies comprising said fusion protein is taught)

wherein said nucleic acid molecule comprises an genomic DNA fragment or EST sequence derived from a eukaryotic organism (Antibodies (also known as immunoglobulins, abbreviated (Ig) are gamma globulin proteins that are found in vertebrates, and are used by the immune system to identify and neutralize foreign objects. Thus by teaching antibody fragment that are made in vertebrates (eukaryotes) Ge et al. inherently teach wherein said nucleic acid molecule comprises an genomic DNA fragment derived from a eukaryotic organism) that is 200 to 1500 base pairs long (a quick search in wikipedia for size of various antibody fragments gave following information: The Ig monomer is a "Y"-shaped molecule that consists of four polypeptide chains; two identical *heavy chains* and two identical *light chains* connected by disulfide bonds. Each chain is composed of structural domains called Ig domains. These domains contain about 70-110 amino acids and are classified into different categories (for example, variable or IgV, and constant or IgC) according to their size and function. There are five types of mammalian Ig heavy chain denoted by the Greek letters: α, δ, ε, γ, and μ.[3] Distinct heavy chains differ in size and composition; α and γ contain approximately 450 amino acids, while μ and ε have approximately 550 amino acids.[3] Thus sizes of 70 to 550 amino acids associated with different antibody fragments taught above translate into 210 to 1650 nt long nucleic acid sequences that encode these. Wikipedia referenced following reference : Janeway CA, Jr

et al (2001). *Immunobiology.* (5th ed.). Garland Publishing. ISBN 0-8153-3642-X in sections where size of antibodies is described. Thus by teaching antibody fragments Ge et al. inherently teach 200 to 1500 base pairs long eukaryotic genomic fragments)

wherein the nucleic acid sequence does not comprise a nucleic acid sequence encoding a signal sequence for the transport of the fusion protein to the periplasm of E. Coli, (see page 233 figure legend of Fig 8-2 (c))

(b) isolating said inclusion bodies (see page 258 section expression of antibody fragment. Specially page 259 protocol 5: refolding of scFv fragments from inclusion bodies steps 1- 5 where isolating said inclusion bodies is taught) ; and

(c) solubilising said fusion protein under suitable conditions (see page 250 step 7 and page 261 steps 8-9 where solubilising said fusion protein under suitable conditions is taught).

Regarding claim 40 Ge et al. teach constructs for producing the fusion antibodies as inclusion bodies in the cytoplasm of E.coli (see page 260 figure 8-8 where vector for inclusion body formation is taught) but do not teach the construct where the fragment of interest are linked to a nucleic acid sequence that encodes the first N-terminal domain of the geneIII protein of filamentous phage.

Regarding claim 40 Krebber et al. teach the construct where the fragment of interest are linked to a nucleic acid sequence that encodes the first N-terminal domain of the geneIII protein of filamentous phage (See the adapter molecule

shown in page 608, Fig. 1 c; and the fusions of gene III protein domains N1 and N1-N2 respectively fused to polypeptide SGCPHHHHHH (see page 610 Fig. 3d and Fig. 3d legend). The letters SGCPH represent the amino acids according to the standard single amino acid abbreviations used in the art. The figure shows the amino acid representation but the Figure 3 legend clearly describes how the nucleic acid constructs were made from starting from fd-phage fCKC construct. These nucleic acid constructs were used to express the gIIIpN1-SGCPHHHHHH and gIIIpN1-N2-SGCPHHHHHH fusions as inclusion bodies in *E.coli* (see page 616 section production of gIIIp domains and coupling to antigen par. 1 where expression of fusion protein as inclusion bodies is taught).

Krebber et al. also teach fusion of gene coding for enzyme β lactamase designated bla gene to N-terminal domain of the gene III (see page 610 fig. 3 c construct labeled N1-Bla-CT).

It would have been prima facie obvious to one of ordinary skill at the time the invention was made to fuse the antibody fragments taught by Ge et al. to the gIIIpN1 or gIIIpN1-N2 construct taught by Krebber et al. The construct taught by Krebber et al. illustrates that it is possible to create a fusion protein comprising the first N-terminal domain of the gene III protein of filamentous phage and a polypeptide encoded by a nucleic acid sequence comprised in a genomic DNA and have this fusion protein accumulate in cytoplasm as inclusion bodies. Instead of β lactamase gene which is of bacterial origin one of ordinary skill in the art can fuse the antibody fragments taught by Ge et al. to the N-terminal domain of the gene III protein and have a reasonable expectation of success in being

able to express these antibody fragments as inclusion bodies in the cytoplasm of *E.coli* because such constructs lack the signal sequences of gIIIp that transport the fusion proteins to peripalsm of *E.coli* cell.

Effectively this gIIIp fusion vector taught by Krebber et al. is equivalent of the inclusion body accumulation vector taught by Ge et al. in the sense both vectors lack signal sequences thus ensuring that the expressed protein will accumulate in the cytoplasm of *E.coli* as inclusion bodies. Once the protein has accumulated as inclusion body Ge et al. teach in detail how to isolate the inclusion bodies and solubilize them under suitable conditions. So one of ordinary skill in the art has reasonable expectation of being able to highly express any genomic fragment encoding various parts of antibodies as gIIIp fusions and accumulate them as inclusion bodies in *E.coli* and then subsequently be able to purify these inclusion bodies from the *E.coli* cells as taught by Ge et al. Using the principles applied for purification and refolding the proteins from the inclusion bodies (see Ge et al.) one of ordinary skill in the art will be able to produce a large amount of pure functional antibody using the bacterial expression system that will also be correctly folded.

Art Recognized Equivalence for the Same Purpose

SEE MPEP 2144.06 Art Recognized Equivalence for the Same Purpose [R-6] < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be

based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Conclusion

7. Claim 40 is rejected over prior art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1637

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